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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/814,873	12/24/91	NAYNER	E CYTE-1-6162
		18M2/0314	GAMBEL, P EXAMINER
			ART UNIT 20 PAPER NUMBER 1606
			DATE MAILED: 03/14/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined Responsive to communication filed on 14/10/93 This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- Notice of References Cited by Examiner, PTO-892.
- Notice of Art Cited by Applicant, PTO-1449.
- Information on How to Effect Drawing Changes, PTO-1474.
- Notice of Draftsman's Patent Drawing Review, PTO-948.
- Notice of Informal Patent Application, PTO-152.
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Part II SUMMARY OF ACTION

- Claims 1-5, 32, 34-76 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
- Claims 6-31, 33, 37-62 have been cancelled.
- Claims _____ are allowed.
- Claims 1-5, 32 are rejected.
- Claims _____ are objected to.
- Claims _____ are subject to restriction or election requirement.
- This application has been filed with Informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
- Formal drawings are required in response to this Office action.
- The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
- The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been approved by the examiner; disapproved by the examiner (see explanation).
- The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).
- Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.
- Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
- Other

15. Claims 6-31, 33 and 37-63 have been canceled.
Claims 1 and 32 have been amended
Claims 1-5, 32 and 34-36 are pending.

16. The IDS, filed 6/14/93 (Paper No. 17), has not been considered since it appears that no references have been submitted.

**REJECTION WHICH STILL REMAIN AND
RESPONSE TO APPLICANT'S ARGUMENTS**

17. Applicant has amended the specification to include the priority under 35 U.S.C. § 120 based upon parent USSN 07/402,389.

18. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 16. Applicant will submit formal drawings upon the indication of allowable subject matter.

19. Applicant has corrected the objections to the disclosure for informalities and for compliance with 37 CFR 1.821(d).

20. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

21. Claims 1-5, 32 and 34-36 stand rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. The specification fails to establish the utility of the claimed $\alpha 4\beta 1$ -specific antibodies as therapeutic agents to block lymphocyte adherence and migration in human patients. Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. It is well known in the art that the jump from such in vitro assays and in vivo animal studies to in vivo human efficacy is a major barrier indeed. This is succinctly summed up by the recent meeting report by Harris et al. which states that

there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses. (page 42, column 3). Waldmann teaches that effective therapy using monoclonal antibodies in the therapy of human diseases due to the pharmacokinetic properties of rodent antibodies in human and human anti-mouse antibody responses. Waldmann also indicates that hopes for antibody-based treatment methods engendered by in vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Even chimeric or humanized antibodies present serious problems with immuno-genicity, since the idiotype of such antibodies contain unique amino acid sequences. Therefore, it does not appear that the asserted utility of the claimed method for treating humans would be believable *prima facie* to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01 (p).

Applicant's arguments have been fully considered but are not found convincing. Applicant argues that Waldmann, Harris et al. in addition Thorpe show that the clinical utility of monoclonal antibodies is believable to persons skilled in the art. Applicant argue that showing in vitro data obtained using monoclonal antibodies and human cells would clearly indicate the clinical utility of the claimed invention. In vitro assays cannot duplicate the complex conditions of in vivo therapy, particularly as they relate to immunotherapeutic reagents. The therapeutic indices of immunotherapeutic drugs such as antibodies have been species- and model-dependent. Further, applicant's claims drawn to murine antibodies would not be expected to work in vivo for the art-accepted reasons of record, that is, primarily HAMA responses. Although humanized antibodies have shown better pharmacokinetics than murine monoclonal antibodies, even these humanized antibodies have been shown to elicit immune responses. Case law has established that utility must be definite and in currently available form, not based on mere assertion. Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). Where the asserted utility would not be believable on its face to persons skilled in the art in view of the contemporary knowledge in the art at the time the application was filed, as is the case here; the burden is upon the applicant to provide proof of the utility of the claimed invention. The examiner does acknowledge that there is great promise for antibodies in human therapy, as indicated by the cited references; however it remains clear that the art including the cited references recognize the clinical reality that this promise has been largely disappointing. These citations are written in terms of promise and potential, not efficacious working examples in humans. Although there have been numerous working examples of antibody-mediated effects both in

vitro and in animal models, only two antibodies have been approved by the FDA for human therapy. The Patent Office does not require the same extensive clinical trials as the FDA, but can require working examples if there is strong evidence that the claimed invention does not work. Human therapy is commensurate with the scope of the claims and is the intended utility of the claimed invention. Successful human treatment with antibodies requires human clinical examples. There is no positive evidence that the methods of the claimed invention would work as human therapy. Furthermore, the chronic and complicated nature of the disorders targeted by the claimed methods makes the provision of positive working examples even more compelling. There is no evidence that $\alpha 4\beta 1$ -specific antibodies can inhibit leukocyte adherence and migration in humans. Applicant's arguments are not found persuasive. The rejection is maintained.

21. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

Applicant has not disclosed how to use $\alpha 4\beta 1$ -specific antibodies therapeutically in humans. There is insufficient written description of the invention with respect to the in vivo operability of $\alpha 4\beta 1$ -specific antibodies to use applicant's invention for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see paragraph 20). Although $\alpha 4\beta 1$ -specific antibodies have been able to block lymphocyte adhesion to endothelial cells in vitro to some degree (see Table IX), no examples have appeared in the application of $\alpha 4\beta 1$ -specific immunotherapy in vivo. It is not clear from the specification whether $\alpha 4\beta 1$ -specific antibodies can inhibit lymphocyte adherence or migration in humans and to what degree. Therefore, it does not appear that the asserted operability of the claimed method and compositions for inhibiting lymphocyte adherence and migration in vivo in humans would be believable *prima facie* to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue

experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

Claims 1-5, 32 and 34-36 stand rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth above in the objection to the specification.

Applicant's arguments and the examiner's rebuttal are the same as set forth in section 20 above. Applicant's arguments have been fully considered but are not found convincing. The rejection is maintained.

22. The previous rejection of claims 1-5 and 32-36 under 35 U.S.C. § 112, first paragraph, for not fulfilling the deposit of biological materials is withdrawn in response to submitting the appropriate declaration.

The Hennings delcaration under 37 C.F.R. § 1.132 filed 12/10/93 is sufficient to overcome the rejection of claims 1-5 and 32-36 based upon 35 U.S.C. § 112, first paragraph.

23. Claims 1-5, 32 and 34-36 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 32 and 34-36 are indefinite in the recitation of an antigen-binding "region" because the characteristics of the "region" defined by claims 1-5, 32 and 34-36 are not known. "Region" is ill-defined and could be any peptide that binds $\alpha 4\beta 1$. No direction or guidance is provided to assist one skilled in the art in the selection of such "regions" nor is there evidence provided that such "regions" would be therapeutically effective. It appears that undue experimentation would be required of one skilled in the art to practice the method of claims 1-5 and 32-36 using the teaching of the specification alone. It is suggested that "antigen-binding fragments" would be a clearer term.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

Applicant has amended the claims to read on "an antigen-binding region" to overcome the previous rejection, however "region" is similarly rejected. Again, applicant is requested to amend the claims to read "antigen-binding fragments".

24. The previous rejection of claim 32 under 35 U.S.C. § 112, first and second paragraphs, has been withdrawn in response to applicant's amended claim.

25. The previous rejection of claims 1-4 and 32-35 under 35 U.S.C. § 103 as being unpatentable over Shimizu et al. in view of Carlos et al., Wayner et al. and Carter et al. has been withdrawn in response to applicant's now-claimed priority to parent USSN 07/402,389.

26. The previous rejection of claims 1-4 and 32-35 under 35 U.S.C. § 103 as being unpatentable over Hemler (Immunol. Today) in view of Stoolman (Cell) and Pitzalis et al. (Eur. J. Immunol.) have been withdrawn in response to applicant's arguments.

27. No claim is allowed.

28. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

29. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

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30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

P
Phillip Gambel, Ph.D.
March 11, 1994

David Lacey
DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
3/11/94